NR 2002:2

The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals and The Dutch Expert Committee on Occupational Standards

129. Chlorotrimethylsilane

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Nordic Council of Ministers

ARBETE OCH HÄLSA | VETENSKAPLIG SKRIFTSERIE

ISBN 91-7045-630-5 ISSN 0346-7821 http://www.niwl.se/

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ARBETE OCH HÄLSA

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National Institute for Working Life
S-112 79 Stockholm
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ISBN 91–7045–630–5
ISSN 0346–7821
http://www.niwl.se/
Printed at Elanders Gotab, Stockholm

Preface

An agreement has been signed by the Dutch Expert Committee on Occupational Standards (DECOS) of the Health Council of the Netherlands and the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG). The purpose of the agreement is to write joint scientific criteria documents which could be used by the national regulatory authorities in both the Netherlands and in the Nordic countries.

The document on health effects of chlorotrimethylsilane was written by Hans Stouten, Fons Rutten, Iris van de Gevel, and Flora de Vrijer from the Toxicology Division of the TNO Nutrition and Food Research Institute, Zeist, the Netherlands and has been reviewed by DECOS as well as by NEG.

The document has been adapted to the different formats used by DECOS and NEG.

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Chairman
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Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
CI	confidence interval
EC	European Commission
IUCLID	International Uniform Chemical Information Data base
LC_{50}	lethal concentration for 50% of the exposed animals at single administration
LD_{50}	lethal dose for 50% of the exposed animals at single administration
LD_{Lo}	lowest observed lethal dose
MTD	maximum tolerated dose
SCE	sister chromatid exchange

Contents

1. Introduction

Chlorotrimethylsilane is a colourless liquid with a sharp hydrogen chloride-like odour. The vapour of chlorotrimethylsilane is heavier than air, travels along surfaces, and the liquid substance can be ignited from distance. At elevated temperatures or during combustion, the substance decomposes producing corrosive and toxic vapours. It violently reacts with water producing hydrogen chloride causing a fire and explosion hazard. Hydrogen chloride is also released upon contact with surface moisture.

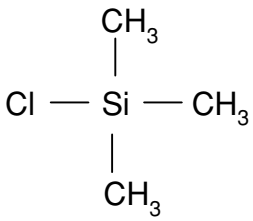
Chlorotrimethylsilane is used as an intermediate in the production of silicone fluids, as a silylating agent, and as a catalyst for propylene oxide production.

Because of the high reactivity, chlorotrimethylsilane is manufactured, stored, and used in airtight, highly specialised installations.

2. Identity, properties, and monitoring

2.1 Identity

2.1.1 Structure



2.1.2 Chemical names and synonyms/registry numbers

Chemical name:	chlorotrimethylsilane
CAS registry no:	75-77-4
Synonyms:	trimethylchlorosilane, monochlorotrimethylsilicone, chlorotrimethylsilicane, trimethylsilyl chloride
EINECS no:	200-900-5
RTECS no:	VV2710000

2.2 Physical and chemical properties (3, 4, 17)

Molecular formula:	C_3H_9SiCl
Molecular weight:	108.66
Boiling point (101.3 kPa):	58.0°C
Melting point (101.3 kPa):	-57.7°C
Relative density (water=1):	0.9
Vapour density (air=1):	3.75
Vapour pressure (20°C; 101.3 kPa):	25.3 kPa
Relative density of saturated vapour/air mixture (air=1; 20°C):	1.7
Flashpoint:	-18.0°C
Auto-ignition temperature:	417.0°C
Explosive limits (%, in air):	1.8-6.0
Solubility in water:	vigorous hydrolysis
Solubility in organic solvents:	soluble in benzene, ether, perchloroethylene
Log $P_{octanol/water}$:	3.00
Physical form:	colourless liquid
Odour:	sharp hydrogen chloride-like odour
Conversion factors (20°C; 101.3 kPa):	1 ppm = 4.5 mg/m^3 1 mg/m^3 = 0.22 ppm

The chlorotrimethylsilane vapour is heavier than air, travels along surfaces, and the liquid substance can be ignited from distance. It violently reacts with water producing hydrogen chloride causing a fire and explosion hazard. Hydrogen chloride is also released upon contact with surface moisture, and will corrode most metals and form flammable hydrogen gas. Generally, chlorotrimethylsilane hydrolyses very rapidly to hydrogen chloride and trimethylsilanol, which condenses rapidly to form hexa-dimethyldisiloxane and water. The committees are of the opinion that the presence of hydrogen chloride in air might indicate the presence of accidentally released chloro-trimethylsilane.

At elevated temperatures or combustion, it decomposes producing corrosive and toxic vapours (silicium dioxide, phosgene, hydrogen chloride). It violently reacts with acids, amines, alcohols, and oxidising agents.

2.3 Validated analytical methods

No validated method was found which can be used for the direct determination of chlorotrimethylsilane in air or biological samples. The rapid hydrolysis of chlorotri-methylsilane will complicate its determination.

3. Sources

3.1 Natural occurrence

Chlorotrimethylsilane does not occur naturally.

3.2 Man-made sources

3.2.1 Production

Chlorotrimethylsilane is produced by a Grignard reaction of silicon tetrachloride with methyl-magnesium chloride. Furthermore, chlorotrimethylsilane can be formed in a reaction of silicon metal with methyl chloride at elevated temperature using copper as a catalyst. Thereafter, chlorotrimethylsilane is separated from mixed methylchlorosilanes by fractional crystallisation (13).

According to the International Uniform Chemical Information Data base (IUCLID) Data Sheet (see also Section 7.3), there are five production sites in Europe (excluding the former Soviet Union), three in the USA, and three in Japan. The annual production per European facility through the years 1990-1994 was stated to be in the range of 1-5 kilotonnes, the worldwide production in the range of 15-40 kilotonnes (4).

3.2.2 Uses

Chlorotrimethylsilane is used as an intermediate by the production of silicone fluids (as a chain terminating agent), as a silylating agent, and as a catalyst for the production of propylene oxide (3, 13). According to the IUCLID Data Sheet, the entire European production is used for the manufacture of organosilicic derivatives, mainly polysiloxanes (4).

Because of the high reactivity, chlorotrimethylsilane must be manufactured, stored, and used in airtight, highly specialised installations (4).

4. Exposure

4.1 General population

No quantitative data were found.

However, environmental levels are expected to be negligible. Chlorotrimethylsilane is not a naturally occurring compound, and is produced and used in closed systems at the same facility. When accidentally released into the environment, it will hydrolyse very rapidly to hydrogen chloride and trimethylsilanol, which condenses rapidly to form hexamethyldisiloxane and water (4, 13).

4.2 Working population

No quantitative data were found. As stated before, because of its high reactivity, chlorotrimethylsilane is used in closed systems, and exposure levels may therefore be

negligible. Moreover, because of this high reactivity, in case of exposure, this may be to hydrogen chloride and hexamethyldisiloxane.

No serious industrial hygiene hazards were stated to exist at a United States chlorosilane production plant (13).

5. Toxicokinetics

5.1 Introduction

There is no information found with respect to the toxicokinetics of chlorotrimethylsilane.

Chlorotrimethylsilane will be rapidly hydrolysed upon contact with tissue fluid releasing hydrogen chloride and trimethylsilanol, which condenses to form hexamethyldisiloxane and water (13).

The committees consider trimethylsilanol to be a stable compound that will not be metabolised to a great extent.

In view of the rapid hydrolysis in aqueous environments, it is obvious that toxicokinetic studies, even at low concentrations, are difficult to carry out.

5.2 Absorption

No data available.

Based on physico-chemical properties (i.e. a molecular weight of 109 and a Log $P_{octanol/water}$ of 3) absorption through the skin can be expected. This view is supported by the findings from an acute dermal toxicity study (see Section 6.2.2), although the corrosive nature of chlorotrimethylsilane may have enhanced dermal penetration by breaking down normal barriers.

5.3 Distribution

No data available.

5.4 Biotransformation

No data available.

5.5 Excretion

No data available.

5.6 Biological monitoring

No data available.

6. Effects

6.1 Observations in man

6.1.1 Irritation and sensitisation

Direct contact with chlorotrimethylsilane as a liquid causes severe skin or eye burns (3). Exposure to the vapour irritates mucous membranes. Ingestion causes severe burns of mouth and stomach (3).

6.1.2 Toxicity due to experimental or occupational exposure

No data available.

6.2 Animal experiments

6.2.1 Irritation and sensitisation

Chlorotrimethylsilane causes severe eye irritation in rabbits (grade 9 on a scale from 1 to 10). In addition, severe burns of the cornea and eyelids were observed (13). When 0.005 ml undiluted chlorotrimethylsilane was placed directly on the cornea of one eye of New Zealand white rabbits (n=6), the maximum mean Draize score was 31.5/110 (observed score/highest possible score) at 6 hours. Immediate discomfort, moderate corneal injury, iritis, and moderate to severe conjunctivitis (with necrosis) were reported, most eyes healing by 7 days (i.e. the observation/recording period) (2, 10).

When exposed to vapours, corneal opacity was observed in rats at concentrations of 12 850 mg/m^3 (2855 ppm) and higher, but not at 10 415 mg/m^3 (2314 ppm) (exposure duration: 1 hour) (see also Section 6.2.2) (2, 10). No data on eye irritation were available from a 2-week inhalation study using rats (see Section 6.2.3) (4).

Chlorotrimethylsilane blanches the skin after direct contact, followed by blisters (13). When 0.5 ml undiluted chlorotrimethylsilane was applied under occlusion (for 4 hours) to the clipped, intact dorsal skin of New Zealand white rabbits (n=6), the modified primary irritation index for erythema and oedema (estimated from Draize readings) was 2.2/8.0 (observed score/highest possible score). Necrosis was observed on each animal within 1 hour after contact, accompanied by severe erythema, moderate oedema, and desquamation. The effects persisted through 7 days (i.e. the observation/recording period (2, 10).

No data on sensitisation were found.

Conclusion

Chlorotrimethylsilane causes severe skin and eye irritation. Since the skin effects persisted throughout the observation period, the compound should be considered as corrosive to the skin.

6.2.2 Acute toxicity

The acute toxicity of chlorotrimethylsilane is high after exposure by inhalation, because the vapour strongly irritates mucous membranes. In rats, a 1-hour single

exposure concentration lethal for 50% of the animals (LC_{50}) of approximately 13 175 mg/m^3 (2928 ppm) has been determined after exposing male and female rats (n=5/sex/group) nose-only to vapour concentrations of approximately 10 415, 12 850, 14 790, and 16 840 mg/m^3 (2314, 2855, 3289, 3742 ppm). The mortality observed in a 14-day observation period was 1/10 (female), 3/10 (all females), 10/10, and 10/10 for the 2314-, 2855-, 3289-, and 3742-ppm group, respectively. The animals exposed at the two highest concentrations died on the 1st observation day. Because of this early dying, recording of clinical signs and body weights was limited to the two lower concentration groups showing nasal crust, rough coat as the main signs, and initial body weight loss and decreased total mean body weight gain. At necropsy, major findings included corneal opacity (in the three higher concentration groups) and diffuse or focal dark coloured areas of the lungs (in all treated groups) (8). When exposed to nearly saturated vapours*, all exposed female Sprague-Dawley rats (n=5) died within 12 minutes. Toxic signs reported included lachrymation, hyperactivity, ataxia, and gasping. At necropsy, red patchy lungs and gas-filled stomachs and intestines were seen (2, 10). In mice, mortality was observed at much lower levels. An "absolute lethal concentration" (LC_{100}) of 100 mg/m^3 was reported (18). However, this only figure was presented in a table and not any experimental detail was given. The committees can not assess the significance of this finding and therefore can not draw conclusions about possible differences in susceptibility between rats and mice.

Following oral (gavage) administration of 0.25 ml undiluted chlorotrimethylsilane/kg to fasted male Sprague-Dawley rats, 5/5 animals died within 2-6 days without preceding signs. At necropsy, dark red lungs, liver, kidneys, and adrenals, and ulcerated stomachs were observed. When given samples diluted in Silicone L-45 oil (dose range: 2.0-8.0 ml/kg; n=5/sex/group; observation period: 14 days), the dose that is lethal for 50% of the animals at single administration (LD_{50}) (95% confidence intervals (CI)), as contained sample, was 5.66 (4.11-7.79) and 6.63 (5.67-7.74) ml/kg in male and female animals, respectively. The lowest observed lethal dose (LD_{Lo}) was 2.0 ml/kg. Sluggishness, dyspnoea, rales, salivation, and prostration were observed, and death followed within 30 minutes to 2 days. At necropsy (descendents), red to black stomachs and intestines, white gas in stomachs and thoracic cavities, black stomach contents, blanched livers, and red fluid in thoracic cavities were seen, while survivors did not show gross lesions (2, 10). The difference in results when testing the undiluted or diluted test compound is not uncommon when testing corrosive compounds.

When chlorotrimethylsilane was applied under occlusion (for 24 hours) to the clipped, intact dorsal skin of New Zealand white rabbits (dose range: 1.0-4.0 ml/kg; n=5/sex/group; observation period: 14 days), LD_{50}s were 2.83 (95% CI: 1.56-3.63) and 1.78 (95% CI: 0.84-3.79) ml/kg for male and female animals, respectively. The LD_{Lo} was 1.0 ml/kg. Local effects included erythema, oedema, necrosis, and scabs, systemic effects immediate discomfort, sluggishness, unsteady gait, diarrhoea, and persistent weight loss. Death occurred after 30 minutes to 8 days. At necropsy, livers with pink to dark red areas were seen (2, 10).

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*Approximately 250 000 ppm estimated from the vapour pressure of chlorotrimethylsilane.

An intraperitoneal LD_{Lo} of 750 mg/kg body weight has been reported in mice (12; details not presented).

Conclusion

Based on acute lethality data, the committees consider the toxicity of chlorotrimethylsilane after inhalation to be low in rats.

Based on European commission (EC) criteria, chlorotrimethylsilane would be classified as toxic if swallowed and as harmful in contact with skin.

6.2.3 Repeated dose and carcinogenicity studies

The IUCLID Data Sheet includes one repeated inhalation study in which an unknown number of male and female Sprague-Dawley rats were exposed to approximately 150 mg/m^3 (34 ppm) chlorotrimethylsilane or to approximately 45 mg/m^3 (30 ppm) hydrogen chloride, 6 hours/day, 5 days/week, for 2 weeks. No treatment-related clinical signs were observed, and the study did not show differences between the two exposure groups (4). No more data were presented.

In A/He male and female mice, chlorotrimethylsilane increased both the incidence (approximately 2-fold: 79% versus 37% and 48% in untreated and vehicle-treated controls, respectively) and the multiplicity of lung tumours at the maximum tolerated dose (MTD) level (1000 mg/kg body weight, total dose; 2 intraperitoneal injections; vehicle: tricaprylin). No such effects were noted after injection of a total dose of 200 or 500 mg/kg body weight (time of sacrifice: 24 weeks after 1st injection; point of time of 2nd injection not indicated) (16). Remarkably, these high intraperitoneal doses of chlorotrimethylsilane, which may be very toxic in mice upon acute exposure by inhalation, did not cause immediate death.

No other repeated dose (including reproduction toxicity and carcinogenicity) studies were found.

Conclusion

The toxicity (including reproduction toxicity and carcinogenicity) following repeated dosing of chlorotrimethylsilane cannot be evaluated because of lack of data. Although chlorotrimethylsilane showed some carcinogenic potential in the A/He mouse lung tumour model, the significance of this finding is questionable since this occurred at the MTD only. Furthermore, this model is very sensitive, and a large number of false positives has been found.

6.2.4 Mutagenic and genotoxic activity

A summary of *in vitro* and *in vivo* genotoxicity studies is presented in Table 1.

As to prokaryotic test systems, Mortelmans et al reported a weak positive response in *S. typhimurium* strain TA100 both in the presence and in the absence of a metabolic activation system (liver S9 of rats and hamsters). Maximum responses of approximately 1.5 times the control values were obtained in two out of three trials without metabolic activation, in three out of three trials with induced hamster liver S9, and in one out of two trials with induced rat liver S9. In half of these positive trials (one non-activated, one hamster-liver activated, one rat-liver activated), these

Table 1. Summary of *in vitro* and *in vivo* genotoxicity assays for chlorotrimethylsilane.

Test system	Concentration	Activation	Response	Reference
S. typhimurium	0.001-5 µl/plate	- S9	Negative	(5)
(TA1535, 1537, 1538, 98, 100)	0.001-5 µl/plate	+ S9	Negative	
S. typhimurium	0-1666 µg/plate	- S9	Negative	(9)
(TA1535, 1537, 98)	0-1666 µg/plate	+ S9	Negative	
S. typhimurium	0-1666 µg/plate	- S9	Weakly positive	(9)
(TA100)	0-3333 µg/plate	+ S9	Weakly positive	
S. typhimurium	1.0-100 µg/plate	-S9[a]	Negative	(19)
(TA1535, 1537, 97, 98, 100)	98-6666 µg/plate	+S9[b]	Negative	
E. coli	0.001-5 µl/plate	- S9	Negative	(5)
(W3110)	0.001-5 µl/plate	+ S9	Negative	
S. cerevisiae	0.001-5 µl/plate	- S9	Negative	(5)
(D4)	0.001-5 µl/plate	+ S9	Negative	
Sister chromatid exchange (SCE)	0.02-0.64 µg/ml	- S9	Negative	(5)
(mouse L5178Y lymphoma cells)	0.02-0.64 µg/ml	+ S9	Negative	
Gene mutation	0.02-0.64 µl/ml	- S9	Negative	(5)
(mouse L5178Y lymphoma cells)	0.02-0.64 µl/ml	+ S9	Negative	
Chromosome aberrations	0.02-0.64 µg/ml	- S9	Positive	(5)
(mouse L5178Y lymphoma cells)	0.02-0.64 µg/ml	+ S9	Negative	
Chromosome aberrations	0-74 mg/kg bw	Not relevant	Negative	(6)
(*in vivo*; rat bone marrow cells)	(single; ip)			

[a] TA1537 not tested without S9;

[b] from Arochlor-induced rat and hamster liver (at 10 and/or 30%)

results were seen at the highest non-cytotoxic level only. Results in strains TA1535, TA1537, and TA98 were negative (9). In a separate test, chlorotrimethylsilane was not mutagenic in *S. typhimurium* strain TA100. Tests with other strains (TA1535, TA1537, TA1538, TA98) and with *E. coli* (strain W3110) were negative as well. Hydrogen chloride, trimethylsilanol and hexamethyldisiloxane, hydrolysis products, were not mutagenic in these assays either. All these tests were performed with and without an S9 metabolic activation system (5). Furthermore, chlorotrimethylsilane as well as hydrogen chloride, trimethylsilanol and hexamethyldisiloxane were not mutagenic in *S. cerevisiae* (5).

When tested in mouse L5178Y lymphoma cells, both in the presence and in the absence of a metabolic activating system, chlorotrimethylsilane did not induce gene mutations or sister chromatid exchanges (SCEs), but it did induce a significant increase in the percentage of cells with chromosome aberrations in the absence of the S9-mix. Although in the table in which the chromosome aberration results were presented a dose-related response was indicated, it was stated by the authors, that "non-linear, erratic patterns were associated with cellular response to treatment with trimethylchlorosilane, ..." making the significance of this finding difficult to interpret (5).

Hydrogen chloride did not induce gene mutations, SCEs, and chromosome aberrations. Trimethylsilanol did neither induce gene mutations nor SCEs in the presence of the S9-mix. However, in the absence of the S9-mix, trimethylsilanol induced SCEs and chromosome abberations in mouse lymphoma cells. Hexamethyldisiloxane was negative when tested for gene mutations and SCEs, but produced in the absence of the S9-mix a significant increase in the percentage of aberrant cells at one single dose in the middle of the dose range. Neither chlorotrimethylsilane, nor hydrogen chloride nor hexamethyldisiloxane induced a positive response in the alkaline elution assay in mouse lymphoma cells (5).

Chlorotrimethylsilane did not cause significant increases in chromosome aberrations in bone marrow of rats following single intraperitoneal injections of 0, 19, 37, 74 mg/kg body weight (sampling times at 6, 24, and 48 hours). Hexamethyldisiloxane and trimethylsilanol, injected intraperitoneally, were negative as well (highest dose of hexamethyldisiloxane tested: 1030 mg/kg body weight). Although dose levels were stated to be based on a preliminary MTD-finding study, no data were presented on general or bone marrow toxicity in the bone marrow assay (6).

Conclusion

Chlorotrimethylsilane is not mutagenic in bacteria and yeast *in vitro*. It did not induce gene mutations, SCEs, or DNA damage in mouse lymphoma cells, but it showed some weak potential for inducing chromosome aberrations in these cells.

In vivo, it was negative in a bone marrow chromosome aberration assay in rats at single intraperitoneal doses up to 74 mg/kg body weight.

Hexamethyldisiloxane showed a similar picture: negative in the aforementioned *in vitro* tests, apart from a weakly positive result in the chromosome aberration test, and negative *in vivo* in bone marrow of rats given a single intraperitoneal injection.

Hydrogen chloride was negative in the aforementioned *in vitro* tests (not tested *in vivo*).

6.2.5 Effects on reproduction

No data available.

6.3 Summary

No toxicological data in humans were found in the literature. Severe irritation of skin, eyes (from exposure to the liquid), and mucous membranes (by vapours), and severe burns of mouth and stomach following ingestion were mentioned.

In animals, chlorotrimethylsilane caused severe corrosion (burns and blisters) of eyes (cornea, eyelids) and skin. It was highly toxic in mice, but not in rats after single inhalation exposure.

Chlorotrimethylsilane and hexamethyldisiloxane had no genotoxic properties in bacteria and yeast *in vitro*. In mouse lymphoma cells, they did not cause gene mutations, SCEs, or DNA damage, but showed only some weak potential for inducing chromosome aberrations. Hydrogen chloride was negative when concomitantly tested in all these assays. An *in vivo* chromosome aberration test in

bone marrow of rats was negative at single intraperitoneal doses up to 74 and 1030 mg/kg body weight of chlorotrimethylsilane and hexamethyldisiloxane, respectively.

There are no data from repeated dose toxicity (including reproduction toxicity and carcinogenicity) studies. In a very sensitive model (i.e. lung tumour response in A/He mice), chlorotrimethylsilane increased both the incidence and the multiplicity of lung tumours, but at the MTD only. The relevance of the results is unclear.

7. Existing guidelines, standards, and evaluations

7.1 General population

No guidelines for the general population were found.

7.2 Working population

No occupational standards set by regulatory bodies were available (see Appendix 1).

In European industrial practice, the limit value of hydrogen chloride (7 mg/m^3) is used (4).

7.3 Evaluations

Following "Council Regulation (EEC) 793/93 on the Evaluation and Control of the Risks of Existing Substances" the European chemical industry by means of a lead company is requested to submit data to IUCLID to allow a risk assessment of these chemicals by the member states of the EC. The data base contained a data sheet on chlorotrimethylsilane (last update: December 18, 1995; lead company: Dow Corning Europe). However, these data were not yet evaluated by an EC member state (4).

8. Hazard assessment

8.1 Assessment of health hazard

It is noticed that clorotrimethylsilane is a very reactive compound and, therefore, manufactured, stored, and handled in closed systems. In case of exposure, if any, this may be to its hydrolysis products, hydrogen chloride, trimethylsilanol and hexamethyldisiloxane*.

The available data on chlorotrimethylsilane do not allow a proper health hazard evaluation. In acute experiments severe irritation has been observed, probably as a consequence of rapid hydrolysis to hydrogen chloride. There were no data from repeated dose toxicity (including reproduction toxicity and carcinogenicity) experiments. Based on the genotoxicity data available, the committees do not consider chlorotrimethylsilane (or its hydrolysis products) to be genotoxic (nearly all

* In Appendix 1, an impression of the toxicity of both hydrolysis products is given.

experiments were negative).

8.2 Groups at extra risk

No specific groups at extra risk are identified in the literature.

8.3 Scientific basis for an occupational exposure limit

The toxicological data base is too poor to form a scientific basis for an occupational exposure limit for chlorotrimethylsilane.

8.4 Additional considerations

The committees are of the opinion that it is not possible to use the available data on the toxicity of hydrogen chloride and hexamethyldisiloxane for the evaluation of the toxicity of chorotrimethylsilane, because no data are available on the other (reactive) intermediate trimethylsilanol. The latter compound might cause irritation as well.

9. Recommendations for research

- Evaluation of the toxicity of hexamethyldisiloxane (the major condensation product of chlorotrimethylsilane).
- Data on the metabolic fate of chlorotrimethylsilane at low concentrations.
- 28-day or 90-day inhalation toxicity study.
- Analytical method for determining occupational air levels.

10. Summary

Stouten H, Rutten F, van de Gevel I, de Vrijer F. *The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals and the Dutch Expert Committee on Occupational Standards. 129. Chlorotrimethylsilane.* Arbete och Hälsa 2002;2:1-18.

Chlorotrimethylsilane is a colourless liquid with a sharp hydrogen chloride-like odour. The chlorotrimethylsilane vapour is heavier than air, and travels along surfaces. At elevated temperatures or combustion, the substance decomposes producing corrosive and toxic vapours. It violently reacts with water producing hydrogen chloride. Hydrogen chloride is also released upon contact with surface moisture. Because of the high reactivity, chlorotrimethylsilane must be manufactured, stored, and used in airtight, highly specialised installations. Chlorotrimethylsilane is used as an intermediate in the production of silicone fluids, as a silylating agent, and as a catalyst in the production of propylene oxide.

There were no data available on the toxicokinetics of chlorotrimethylsilane. No methods for monitoring chlorotrimethylsilane in air or biological samples were found.

Chlorotrimethylsilane is a very irritative compound, probably due to its very fast hydrolysis to hydrogen chloride. No toxicological data in humans were found in the literature. Severe irritation of skin, eyes (from exposure to the liquid), and mucous membranes (by vapours), and severe burns of mouth and stomach following ingestion were mentioned. In animals, chlorotrimethylsilane caused severe corrosion (burns and blisters) of eyes (cornea, eyelids) and skin. It was highly toxic in a single study in mice but not in rats upon single inhalation exposure.

Chlorotrimethylsilane had no genotoxic properties in bacteria and yeast *in vitro*. In mouse lymphoma cells, it did not cause gene mutations, SCEs, or DNA damage, but showed some weak potential for inducing chromosome aberrations. An *in vivo* chromosome aberration test in bone marrow of rats was negative at single intra-peritoneal doses up to 74 mg/kg body weight. Hexamethyldisiloxane, a hydrolysis product of chlorotrimethylsilane, showed similar results in these tests. Hydrogen chloride, the other hydrolysis product and included in the *in vitro* tests as well, was negative in all these tests.

There are no data from repeated dose toxicity studies (including reproduction toxicity and carcinogenicity). In a very sensitive model (i.e. lung tumour response in A/He mice), chlorotrimethylsilane increased both the incidence and the multiplicity of lung tumours, but at the maximum tolerated dose only. The relevance of the results is unclear.

10. Summary in Swedish

Stouten H, Rutten F, van de Gevel I, de Vrijer F. *The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals and the Dutch Expert Committee on Occupational Standards. 129. Chlorotrimethylsilane.* Arbete och Hälsa 2002;2:1-18.

Klortrimetylsilan är en färglös vätska med en stickande lukt av klorväte. Ångan är tyngre än luft och transporteras längs ytor. Vid förhöjd temperatur eller vid förbränning bryts substansen ner och bildar frätande och giftiga ångor. Klortrimetylsilan reagerar häftigt med vatten och bildar klorväte. Klorväte frigörs även vid kontakt med ytfukt. På grund av dess höga reaktivitet måste klortrimetylsilan tillverkas, lagras och användas i lufttäta, högt specialiserade anläggningar. Klortrimetylsilan används som intermediär vid tillverkning av silikonoljor, som silylerare och som katalysator vid tillverkning av propylenoxid.

Det saknas data på klortrimetylsilans toxikokinetik liksom metoder för mätning av ämnet i luft eller biologiska medier.

Klortrimetylsilan är mycket irriterande, sannolikt på grund av den snabba hydrolysen till klorväte. Inga toxikologiska humandata har påträffats i litteraturen. Kraftig irritation av hud, ögon (vid exponering för vätska) och slemhinnor (av ånga) samt allvarliga brännskador på mun och magsäck efter förtäring har rapporterats. I djurförsök har klortrimetylsilan orsakat kraftiga frätskador (brännskador och blåsor) på ögon (hornhinna, ögonlock) och hud. Ämnet var mycket toxiskt i en studie på mus men inte på råtta vid engångsexponering via inandning.

Klortrimetylsilan var inte genotoxiskt för bakterier och jäst *in vitro*. Ämnet orsakade inte genmutationer, systerkromatidutbyten eller DNA-skador på muslymfomceller, men uppvisade en svag potential att inducera kromosomaberrationer. Ett kromosomaberrationsförsök *in vivo* på benmärg från råtta var negativt vid intraperitoneala engångsdoser upp till 74 mg/kg kroppsvikt. Hexametyldisiloxan, en hydrolysprodukt av klortrimetylsilan, uppvisade liknande resultat i dessa försök. Klorväte, den andra hydrolysprodukten som också ingick i *in vitro*-försöken, var negativt i alla tester.

Det saknas toxicitetsdata från studier med upprepad dosering (inklusive reproduktionstoxicitet och carcinogenicitet). I en mycket känslig djurmodell (lungtumörsvaret hos A/He-möss) ökade klortrimetylsilan både incidensen och multipliciteten av lungtumörer, men endast vid den maximalt tolerabla dosen. Relevansen av resultaten är oklar.

11. References

1. Badinand MA. Étude toxicologique de quelques dérivés organiques du silicium (silicates, siloxanes, silicones). *Bull Soc Pharm Bordeaux* 1952;90:298-306.
2. Bushy Run Research Centre (BRRC). *Initial submission: organochlorosilane A-161: acute toxicity and primary irritancy studies in rabbits (project report) with cover sheet and letter dated 012492*. Springfield VA, USA: National Technical Information Service (NTIS), 1992; NTIS order no NTIS/OTS0533916.
3. EPA. *Chemical profile: Trimethylchlorosilane*. US Environmental Protection Agency, Washington DC, USA, 1985.
4. European Commission (EC): European Chemicals Bureau - Existing Chemicals. *Chlorotrimethylsilane*. IUCLID Data Sheet. Ispra, Italy: EC - JRC Environment Institute, 1996; CD-ROM, Edition 1 (date of last update chlorotrimethylsilane file: Oct 23, 1995).
5. Isquith A, Matheson D, Slesinski R. Genotoxicity studies on selected organosilicon compounds: in vitro assays. *Food Chem Toxicol* 1988;26:255-261.
6. Isquith A, Slesinski R, Matheson D. Genotoxicity studies on selected organosilicon compounds: in vivo assays. *Food Chem Toxicol* 1988;26:263-266.
7. Kamrin MA. Workshop on the health effects of HCl in ambient air. *Regul Toxicol Pharmacol* 1992;15:73-82.
8. Kolesar GS, Siddiqui WH, Hobbs EB. *A comparison of acute inhalation toxicity of a series of chlorosilanes with hydrogen chloride in rats*. Midland MI, USA: Dow Corning Corporation, Toxicology Department, 1987.
9. Mortelmans K, Haworth S, Lawlor T, Speck W, Tainer B, Zeiger E. Salmonella mutagenicity tests: II. Results from the testing of 270 chemicals. *Environ Mutagen* 1986;8, Suppl. 7:1-119.
10. Myers RC, Ballantyne B. Acute toxicologic evaluation of trimethylchlorosilane. *J Am Coll Toxicol* 1993;12:574.
11. Myers RC, Ballantyne B. Acute toxicologic evaluation of hexamethyldisiloxane. *J Am Coll Toxicol* 1993;12:590.
12. NIOSH. *Registry of Toxic Effects of Chemical Substances (RTECS)*. US Department of Health and Human Services, National Institute of Occupational Safety and Health, CD-ROM, issue January 1998. SilverPlatter International, 1998 (last update chlorotrimethylsilane file: October 1997).
13. NLM. *Hazardous Substances Databank (HSDB)*, US National Library of Medicine, CD-ROM, issue January 1998. SilverPlatter International, 1998 (last update chlorotrimethylsilane file: February 1997).
14. Rowe VK, Spencer HC, Bass SL. Toxicological studies on certain commercial silicones and hydrolyzable silane intermediates. *J Ind Hyg Toxicol* 1948;30:332-352.
15. Scientific Expert Group on Occupational Exposure Limits (SEG). *Recommendation from Scientific Expert Group on Occupational Exposure Limits for hydrogen chloride*. Luxembourg, 1993 (SEG/SUM/49A).
16. Stoner GD, Weisburger EK, Shimkin MB. Tumor response in strain A mice exposed to silylating compounds used for gas-liquid chromatography. *J Natl Cancer Inst* 1975;54:495-497.
17. Stuurgroep Chemiekaarten, eds. Trimethylchloorsilaan. In: *Chemiekaarten: gegevens voor het veilig werken met chemicaliën*. 12th ed. Alphen a/d Rijn, The Netherlands: Samson HD Tjeenk Willink bv, 1996:1070.
18. Voronkov MG, Lukevics E. Biologically active compounds of silicon. *Russian Chem Rev* 1969;38:975-986.
19. Zeiger E, Anderson B, Haworth S, et al Salmonella mutagenicity tetsts: V. Results from the testing of 311 chemicals. *Environ Mol Mutagen* 1992:19, Suppl. 21: 2-141.

12. Data bases used in the search for literature

For the preparation of this document, literature has been retrieved from several data bases using online and CD-ROM systems (last update: May 1998).

Submitted for publication February 22, 2002.

Appendix 1.

Current limit values

No occupational exposure limits/standards for chlorotrimethylsilane are established or recommended in The Netherlands, Germany, the Nordic countries, the United Kingdom, and the USA (ACGIH, NIOSH).

Toxicity data on hydrogen chloride and hexamethyldisiloxane

The next paragraphs are not the result of an extensive literature search but merely meant to give some impression of the toxicity of hydrogen chloride and hexamethyldisiloxane. The data on hexamethyldisiloxane are mainly from abstracts from records of the US EPA's data base TSCATS and were retrieved via Toxline on CD-ROM and via the Right-to-Know Network on the Internet (http://www.rtk.net).

Hydrogen chloride
As to hydrogen chloride, data on effects on humans are from very old reports. Levels above 15 mg/m^3 (10 ppm) were considered to lead to work impairment, and above 75 mg/m^3 (50 ppm) to work hindrance; above 150 mg/m^3 (100 ppm) work would be impossible (7).

In experimental animal studies, the principle effects following acute inhalation exposure to hydrogen chloride (occurring at several thousands of ppm) are irritation of the eyes, respiratory tract, and exposed areas of skin. When rabbits and guinea pigs were exposed to 152 mg/m^3 (100 ppm) hydrogen chloride, 6 hours/day, for 5 days, only slight respiratory difficulties, eye and nasal irritation, and slightly reduced haemoglobin levels were observed. No adverse effects or morphological changes occurred in a monkey, rabbits, and guinea pigs exposed to 46 mg/m^3 (30 ppm), 6 hours/day, for 4 weeks. In a life-time inhalation carcinogenicity study, laryngeal hyperplasia, but no serious nasal epithelial irritation or preneoplastic or neoplastic lesions were seen in rats exposed to 15 mg/m^3 (10 ppm), 6 hours/day, 5 days/week (7, 15).

Hexamethyldisiloxane
Hexamethyldisiloxane did not demonstrate any evidence of sensitisation in a repeated insult patch test with 87 Caucasian females, 2 Hispanic females, and 11 Caucasian males (TSCATS).

In experimental animals, no irritation was observed in two separate studies following single application of hexamethyldisiloxane to the skin of rabbits (11, TSCATS), confirming the negative results of an older study (14). Following repeated application (10 over a 14-day period) to the skin of rabbits, slight irritation was found (TSCATS). When instilled into both eyes of rabbits, the compound was concluded to

be minimally irritating to unwashed eyes and minimally irritating to eyes washed after 1 minute of contact. Severe irritation of the iris and mild to no irritation of the conjunctiva were observed after 1 hour in both eyes, but not at 24 hours and later time points (TSCATS). In another study, hexamethyldisiloxane produced a maximum mean score of 1.8/110 (observed score/highest possible score) at 1 hour. Iritis (in 1/6 rabbits) and minor conjunctivitis were seen but healed by 1-2 days (11). These results concur with those from an older report in which instillation of the test substance produced immediate irritation, which was healed by 1 hour (14).

Hexamethyldisiloxane was not very toxic following single exposures by inhalation, gavage, or dermal application. In rats exposed to "substantially" saturated atmospheres (according to (14), a saturated atmosphere should be at the order of 39 000-40 000 ppm at 21-22°C), the median time for death in 50% of the animals was 15 and 20 minutes for males and females, respectively. The minimum time needed to induce mortality was 13 minutes. Signs observed were hyperactivity followed by hypoactivity, laboured breathing, convulsions, and red discharge from eyes and nose; at necropsy, there were dark red lungs and liver (11). In other experiments, exposure to "substantially" saturated vapours did not induce mortality or toxic signs in animals exposed for 1 hour but caused the death of 2/6 rats after 6 and 7 hours of exposure, respectively, in one study while all rats survived a 6-hour exposure in a second study (TSCATS).

Dermal LD_{50}s of 16.0 and >16.0 ml/kg body weight were reported for male and female rabbits, respectively (11). No mortality or behavioural effects were seen in rabbits following a single dermal dose of 2000 mg/kg body weight (TSCATS).

An oral LD_{50} of >16.0 ml/kg body weight was found in rats (11). Furthermore, it was reported that doses up to 34 600 mg/kg body weight did not induce mortality, behavioural effects, or gross pathological changes (TSCATS).

Following repeated exposure, in rats exposed to 499 or 1004 ppm, 6 hours/day, 5 days/week, for 2 weeks, effects were seen only in the male animals including a dose-related trend toward increased mean kidney weights and a statistically significantly increased relative kidney weight in the high exposure group, corresponding with an increased severity of hyaline droplets in the proximal tubules (TSCATS).

In an older experiment, in which female rats and guinea pigs exposed to 4400 ppm, 7 hours/day, for 15 days over an 18-day period (rats) or for 20 days over a 26-day period (guinea pigs), slightly increased absolute liver and kidney weights and slightly decreased body weight gains were seen in rats and guinea pigs, respectively. No effects were observed upon gross or microscopic examination (14). In guinea pigs exposed to 12 000-15 000 ppm, 30-40 min/day, for 20 days, no mortality was found (1).

In a 28-day dermal toxicity study using rats, non-occlusive application, 6 hours/day, 5 days/week, of doses up to 1000 mg/kg body weight/day only induced decreases in body weight gain and food consumption in weeks 3 and 4 and in absolute liver weights in the male animals given 1000 mg/kg body weight/day (TSCATS).

Trimethylsilanol

Trimethylsilanol was negative in a dominant lethal assay in rats after oral treatment for 5 days per week for 8 weeks (6).

No additional toxicity data were found for trimethylsilanol.